Lipase-catalyzed second-order asymmetric transformations as resolution and synthesis strategies for chiral 5-(acyloxy)-2(5H)-furanone and pyrrolinone synthons

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Supplementary Material

General information. The conversions of the lipase catalyzed (trans)esterifications were measured on a Hewlett Packard 5890 GC, equipped with a 50 m x 0.53 mm HP-1 crosslinked methyl silicon gum column. E.e.'s were determined with a Hewlett Packard 5890 GC, with a capillary column coated with CP cyclodextrin B-2,3,6-M-19 (for furanones) or with a 30 m x 0.25 mm capilary column (ASTEC G9409-15) coated with B-TA (β-cyclodextrin, trifluoroacetyl) (for pyrrolinones). Optical rotations were determined with a Perkin Elmer 241 polarimeter. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. ^{1}H NMR spectra were recorded on a Varian Gemini (at 200 MHz). ^{13}C NMR spectra were recorded on a Varian Gemini 200 (at 50.32 MHz). Chemical shifts are denoted in δ-units (ppm) relative to $CDCl_3$. The splitting patterns are designated as follows: s (singlet); d (doublet); dd (double doublet); t (triplet); q (quartet); m (multiplet) and br (broad). R_f values were obtained by using TLC on silica gel coated plastic sheets (Merck silica gel F_{254}). Merck silica gel 60 (230-400 mesh) was used for filtration and for flash Chromatography. The solvents were distilled and dried, if necessary, using standard methods. Reagents were used as obtained from Acros Chimica, Aldrich, Fluka or Merck, unless otherwise stated. 5-Hydroxy-5H-furan-2-one and 5-Methoxy-5H-furan-2-one were prepared following literature procedures[16].

Propionic acid 5-oxo-2,5-dihydro-furan-2-yl ester (1a). 5-Hydroxy-5H-furan-2-one **5** (4.00 g, 40,0 mmol) and propionic anhydride (5.25 g, 40.3 mmol) were dissolved in 25 ml toluene. A catalytic amount of p-toluene sulfonic acid was added to the mixture. After 24 hours reflux the reaction was complete. Kugelrohr distillation (0.1 mm Hg, 110 °C) afforded

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4.32 g (27.7 mmol, 69% yield) pure product **1a**. ^{1}H NMR ($CDCl_3$): δ 7.33 (dd, J = 5.6 Hz, J = 1.2 Hz, *H*C=CHCO); 6.98 (d, J = 1.4 Hz, C*H*); 6.28 (dd, J = 5.6 Hz, J = 1.2 Hz, HC=C*H*CO); 2.40 (q, J = 7.6 Hz, CH_2CH_3); 1.13 (t, J = 7.6 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 172.38 (s, HC=CH*C*OOR); 169.18 (s, CH_3CH_2 *C*OOR); 149.95 (d, *C*=C), 125.02 (d, C=*C*); 93.42 (d, *C*H); 27.19 (t, CH_2); 8.56 (q, CH_3). Anal. cald for $C_7H_8O_4$: C 53.86; H 5.16; O 40.98, found: C 53.51; H 5.24; O 41.90.

Acetic acid 5-oxo-2,5-dihydro-furan-2-yl ester (1b)[17]. 5-Hydroxy-5H-furan-2-one **5** (22.8 g, 227 mmol) was added to acetic acid anhydride (24.8 g, 242 mmol). A catalytic amount of p-toluene sulfonic acid was added to the mixture and the solution was heated to 50°C in an oil bath. After 2.5 hours the product was distilled off, giving a pale yellow oil **1b** (29.0 g, 204 mmol, 90% yield), bp 102-104 °C, 0.05 mm Hg. ^{1}H NMR ($CDCl_3$): δ 7.32 (dd, J = 5.6 Hz, J = 1.3 Hz, *H*C=CHCO); 6.95 (d, J = 1.2 Hz, C*H*); 6.30 (dd, J = 5.6 Hz, J = 1.3 Hz, CH=C*H*CO); 2.13 (s, CH_3). ^{13}C NMR: δ 168.90 (s, HC=CH*C*O); 169.5 (s, H_3CCOOR); 149.80 (d, *C*=C); 125.09 (d, C=*C*); 93.76 (d, *C*H); 20.56 (q, CH_3). Anal. cald for $C_6H_6O_4$: C 50.72; H 4.25; O 45.03, found: C 50.52; H 4.28; O 45.33.

Acetic acid 1-methyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl ester (7). First 5-hydroxy-1-methyl-1,5-dihydro-pyrrol-2-one **11** was synthesized by a slightly modified literature procedure[18]. A solution of N-methylpyrrole (3.00 g, 37.0 mmol) in 400 mL of water was placed in a water-cooled reaction vessel. A stream of oxygen was introduced through a glass filter (P2) in the bottom of the vessel. A sheet of kapton was used as an U.V. filter and a high-pressure sodium lamp (Philips SON 150 W) served as the light source. The mixture was irradiated for 3 h and every 30 min a few drops of a concentrated Methylene Blue solution were added. The dark solution was stirred with norit and filtered over celite. The solvent was

removed below 40 °C and the brown oil was extracted with dichloromethane, dried ($MgSO_4$) and concentrated in vacuo. The solid was dissolved in acetone, stirred with norit, filtered over celite and concentrated in vacuo, yielding an almost pure product **11** (1.42 g, 12.6 mmol, 34% yield), mp 78-80 °C. ^{1}H NMR ($CDCl_3$): δ 2.92 (s, 3H, NC*H*$_3$); 5.19 (br s, 1H, O*H*); 5.32 (s, 1H, OC*H*N); 6.05 (d, J = 5.9 Hz, 1H, CH=C*H*CO); 6.95 (d, J = 5.9 Hz, 1H, C*H*=CHCO). ^{13}C NMR ($CDCl_3$): δ 25.34 (q, N*C*H$_3$); 84.44 (d); 127.53 (d); 146.07 (d); 167.71 (s); 169.70 (s). A solution of **11** (2.25 g, 19.9 mmol) and acetic anhydride (2.05 g, 20.1 mmol) in pyridine (35 mL) was stirred at room temperature for 18 h. The solution was concentrated in vacuo at room temperature. The resulting brown oil was filtered over silica and concentrated in vacuo. After Kugelrohr distillation (0.1 mm Hg, 100 °C), **7** (2.46 g, 15.9 mmol, 80% yield) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H, OCOC*H*$_3$); 2.93 (s, 3H, NC*H*$_3$); 6.26 (d, J = 6.0 Hz, 1H, CH=C*H*CO); 6.44 (s, 1H, OC*H*N); 6.97 (dd, J = 6.0, 1.7 Hz, 1H, C*H*=CHCO). ^{13}C NMR ($CDCl_3$): δ 20.67 (q, OCO*C*H$_3$); 26.59 (q, N*C*H$_3$); 83.91 (d); 129.85 (d); 141.80 (d); 169.62 (s); 170.31 (s). Exact mass calcd for $C_7H_9NO_3$: 155.058, found: 155.058.

5-Hydroxy-1,5-dihydro-pyrrol-2-one (12). The literature procedure[19] was slightly modified and scaled up. To an ice-cooled aqueous ammonia solution (1 L) 5-methoxy-5H-furan-2-one (50.0 g, 439 mmol) was added over 15 min. After 1h of stirring the reaction was complete (disappearance of methoxyfuranone was followed by TLC: ethyl acetate, R_f 0.67). The reaction mixture was concentrated under reduced pressure, the temperature not exceeding 25 °C. The yellow product was dissolved in 100 mL of water and freeze-dried for 48 h yielding **12** as a light-yellow powder (44.7 g, 451 mmol, 103 % yield). It was not purified further. ^{1}H NMR (DMSO-d_6): δ 5.43 (m, 1H, OC*H*N); 5.98 (m, 2H, CH=C*H*CO, O*H*); 6.97 (m, 1H, C*H*=CHCO); 8.37 (br s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 80.17 (d); 127.50 (d);

149.58 (d); 171.99 (s).

Acetic acid 1-acetyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl ester (2). To an ice-cooled mixture of crude 5-hydroxy-1,5-dihydro-pyrrol-2-one (obtained from 10.0 g, 87.7 mmol of methoxyfuranone), DMAP (1.07 g, 8.77 mmol) and pyridine (80 mL), acetic anhydride (22.4 g, 219 mmol) was added slowly. After one night of stirring at room temperature the reaction was complete (as judged by ^{1}H NMR) . Water (300 mL) was added and the solution was concentrated in vacuo, the temperature not exceeding 25 °C. Toluene (100 mL) was added and it was concentrated in vacuo again. The dark brown solid was dissolved in dichloromethane and filtered over silica. The yellow solution was concentrated in vacuo and the residue was recrystallized from acetone to give pure **2** (9.34 g, 51.0 mmol, 58% yield starting from methoxyfuranone) as white crystals, mp 98°C. ^{1}H NMR ($CDCl_3$): δ 2.11 (s, 3H, OCOC*H*$_3$); 2.54 (s, 3H, NCOC*H*$_3$); 6.25 (d, J = 5.9 Hz, 1H, CH=C*H*CO); 7.12 (d, J = 2.1 Hz, 1H, OC*H*N); 7.18 (dd, J = 6.0, 1.9 Hz, 1H, C*H*=CHCO). ^{13}C NMR ($CDCl_3$): δ 20.29 (q, OCO*C*H$_3$); 24.25 (q, NCO*C*H$_3$); 80.03 (d); 128.53 (d); 144.90 (d); 168.01 (s); 168.60 (s); 169.24 (s). Anal. calcd for $C_8H_9NO_4$: C 52.46; H 4.95; N 7.65, found: C 52.36; H 4.93; N 7.62.

Propionic acid 5-oxo-1-propionyl-2,5-dihydro-1H-pyrrol-2-yl ester (8). The procedure described above for **2** was followed, starting from crude **12** (obtained from 5.00 g, 43.9 mmol of methoxyfuranone), using propionic anhydride (14.3 g, 110 mmol). After Kugelrohr distillation (0.01 mm Hg, 140°C) **8** (6.48 g, 30.7 mmol, 70% yield starting from methoxyfuranone) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.09 (t, J = 7.5 Hz, 3H); 1.10 (t, J = 7.4 Hz, 3H); 2.31 (dq, J = 7.5, 3.2 Hz, 2H, OCOC*H*$_2$); 2.87 (q, J = 7.2 Hz, 2H, NCOC*H*$_2$); 6.16 (d, J = 5.6 Hz, 1H, CH=C*H*CO); 7.09 (m, 2H, OC*H*N, C*H*=CHCO).^{13}C

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NMR ($CDCl_3$): δ 7.65 (q, $NCOCH_2CH_3$); 8.56 (q, $OCOCH_2CH_3$); 27.02 (t, $OCOCH_2$); 29.99 (t, $NCOCH_2$); 80.22 (d); 128.69 (d); 145.01 (d); 168.13 (s); 172.63 (s); 172,90 (s). Exact mass calcd for $C_{10}H_{13}NO_4$: 211.084, found: 211.084.

Acetic acid 5-oxo-1-propionyl-2,5-dihydro-1H-pyrrol-2-yl ester (9). The procedure described above for **2** was followed, starting from crude **12** (obtained from 5.00 g, 43.9 mmol of methoxyfuranone), not using DMAP. After recrystallization from acetone acetic acid 5-oxo-2,5-dihydro-1H-pyrrol-2-yl ester **13** (1.78 g, 12.7 mmol, 29% yield starting from methoxyfuranone) was obtained as white crystals, mp 127 °C. ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $OCOCH_3$); 6.17 (d, J = 5.7, 1H, CH=C*H*CO); 6.26 (s, 1H, OC*H*N); 6.94 (m, 1H, C*H*=CHCO); 7.43 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 20.74 (q, $OCOCH_3$); 80.17 (d), 129.87 (d); 144.09 (d); 171.00 (s); 171.98 (s). Anal. calcd for $C_6H_7NO_3$: C 51.06; H 5.00; N 9.92, found: C 50.84; H 5.01; N 9.86. The procedure described for **2** was followed again, starting from **13** (1.38 g, 9.76 mmol), using DMAP (0.12 g, 0.98 mmol) and propionic acid (1.91 g, 14.7 mmol). After Kugelrohr distillation (0.01 mm Hg, 50 °C), **9** (1.63 g, 8.27 mmol, 85% yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.04 (t, J = 7.3 Hz, 2H, $NCOCH_2CH_3$); 1.98 (s, 3H, $OCOCH_3$); 2.81 (q, J = 7.2 Hz, 2H, $NCOCH_2$); 6.12 (d, J = 6.1 Hz, 1H, CH=C*H*CO); 7.00 (d, J = 2.2 Hz, 1H, OC*H*N); 7.06 (dd, J = 6.0, 2.1 Hz, 1H, C*H*=CHCO). ^{13}C NMR ($CDCl_3$): 7.65 (q, $NCOCH_2CH_3$); 20.44 (q, $OCOCH_3$); 30.00 (t, $NCOCH_2$); 80.27 (d); 128.75 (d); 144.87 (d); 168.10 (s); 169.42 (s); 172.68 (s). Exact mass calcd for $C_9H_{11}NO_4$: 197.069, found: 197.068.

Propionic acid 1-acetyl-5-oxo-2,5dihydro-1H-pyrrol-2-yl ester (10). The procedure described above for **2** was followed, starting from 1-Acetyl-5-hydroxy-1,5-dihydro-pyrrol-2-one **6** (0.24 g, 1,72 mmol, obtained from the transesterification), using propionic anhydride

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(0.23 g, 1.74 mmol), but no DMAP. After filtration over silica **10** (0.30 g, 1.52 mmol, 88 % yield) was obtained as a white solid, mp 90-91 °C. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 7.5 Hz, 3H, $OCOCH_2CH_3$); 2.34 (dq, J = 7.5, 2.8 Hz, 2H, $OCOCH_2$); 2.49 (s, 3H, $NCOCH_3$); 6.21 (d, J = 6.0 Hz, 1H, CH=C*H*CO); 7.09 (d, J = 1.7 Hz, 1H, OC*H*N); 7.14 (d, J = 6.0 Hz, C*H*=CHCO). ^{13}C NMR ($CDCl_3$): 8.68 (q, $OCOCH_2CH_3$); 24.45 (q, $NCOCH_3$); 27.11 (t, $OCOCH_2$); 80.14 (d); 128.54 (d); 145.01 (d); 168.05 (s); 168.65 (s); 172.84 (s). An analytical sample was recrystallized from TBME. Anal. calcd for $C_9H_{11}NO_4$: C 54.82; H 5.62; N 7.10, found: C 54.77; H 5.74; N 7.15.

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